REMARKS/ARGUMENTS

I. Title

The Examiner has objected to the title of the invention as "not descriptive", and has required a new title that is clearly indicative of the invention to which the claims are directed. In particular, it is the Examiner's position that, contrary to the original title "METHOD FOR SELF-VALIDATION OF MOLECULAR MODELING", there is no "self" validation cited in the claimed invention. Applicants have amended the title to "METHOD FOR VALIDATING COMPUTER MODELING OF A MOLECULAR SYSTEM", and submit that the amended title is descriptive of the claimed invention.

II. Rejections under 35 U.S.C. §101

The Examiner has rejected Claims 1-8 and 10-20 under 35 U.S.C. §101, asserting that the claimed invention is directed to non-statutory subject matter. It is the Examiner's position that the rejected claims are directed to non-statutory subject matter because they are directed to computer implemented methods of validation without requiring the performance of a result outside of the computer and thus manipulate concepts or convert data without resulting in any physical transformation outside of the computer.

Applicants respectfully disagree, for at least the following reasons. Firstly, in supporting the rejection, the Examiner has applied only the first of two alternative tests under the "Safe Harbors" in MPEP 2106(IV)(B)(2)(b)(i). This first test characterizes a process as statutory if the process requires physical acts to be performed outside the computer. Even assuming, *arguendo*, that the "testing" step in the rejected claims is not worded so as to be directed to physical testing per se (and thus, according to the Examiner's reasoning, fails to qualify as the performance of a result outside of the computer), the claims are nevertheless directed to statutory subject matter because, among other things, they qualify for the second test in the Safe Harbor (*supra*).

The second Safe Harbor test characterizes a process as statutory if it requires the measurements of physical objects or activities to be transformed outside of the computer into

computer data, where the data comprises signals corresponding to physical objects or activities external to the computer system, and where the process causes a physical transformation of the signals which are intangible representations of the physical objects or activities.

The rejected claims are all directed to methods for validating a computer modeling of a molecular system. Computer models of molecular systems involve molecular mechanics or molecular dynamics simulations of the behavior of individual molecules, which are physical objects. Such simulations therefore manipulate data representing physical objects. The data manipulated typically include the identity of the atoms being simulated, the molecular weights of the atoms, the nature of the chemical bonds linking the atoms to one another, the angles and lengths of the bonds, the electrostatic charge distribution on the connected atoms, and the like. Although these parameters are microscopic in nature, they are determined using physical measurements, with experimental techniques such as spectroscopy (e.g., NMR), X-ray diffraction, and the like.

The claimed methods expressly recite "selecting a model parameter", where the model is a representation or function of measured physical properties such as those exemplified in the above paragraph. The parameters are used in a molecular simulation, and used to determine the value of the validation measure. Accordingly, the invention as claimed manipulates data representing physical objects or tangible materials, and falls within the second of the two alternative tests of processes qualifying for the Safe Harbor referenced above, which in turn is based on decisions of the CCPA and the Federal Circuit, including, e.g., *Arrhythmia* (958 F.2d at 1056, 22 USPQ2d at 1036).

Secondly, the claims at issue are limited to a practical application within the technological arts. All of the rejected claims are directed to methods of validating a computer modeling of a molecular system. As detailed above, computer models of molecular systems are a specific research tool used by scientists (e.g., structural and medicinal chemists) to help understand the properties and behavior of molecules they are studying. For example, molecular modeling is commonly applied to proteins, in particular to proteins constituting therapeutic "targets" used by pharmaceutical companies in the

development of new drugs. Such techniques are playing an increasingly-important role in drug discovery. Methods for validating such simulation models are therefore directly applicable to the technological arts and thus constitute statutory subject matter.

As the Federal Circuit stated in *AT&T v. Excel Communications, Inc.*, (172 F.3d 1352, 50 USPQ2d 1447 (Fed. Cir. 1999)):

> This court recently pointed out that any step-by-step process, be it electronic, chemical, or mechanical, involves an "algorithm" in the broad sense of the term. See *State Street Bank & Trust Co. v. Signature Fin. Group, Inc.*, 149 F.3d 1368, 1374-75, 47 USPQ2d 1596, 1602 (Fed. Cir. 1998), cert. denied, - U.S. -, 119 S. Ct. 851 (1999). Because § 101 includes processes as a category of patentable subject matter, the judicially-defined proscription against patenting of a "mathematical algorithm," to the extent such a proscription still exists, is narrowly limited to mathematical algorithms in the abstract.

As discussed above, the present invention is a specific process useful in the simulation or modeling of molecules, and is in no way a "mathematical algorithm in the abstract".

In view of the foregoing, the Applicants respectfully submit that the rejection of Claims 1-8 and 10-20 under 35 U.S.C. §101, is inappropriate and should be withdrawn.

III. Rejections under 35 U.S.C. §102(e)(2) -- Sardashi, et al., P/N 6,208,137

The Examiner rejected Claims 1, 5, 7, 9, 10, 16-18, and 20 under 35 U.S.C. §102(e)(2) as anticipated by Sardashi, et al., P/N 6,208,137.

Methods of the Present Invention

All claims rejected by the Examiner as anticipated by Sardashi, et al., are directed to methods for validating a computer modeling of a molecular system. One group of claims includes the steps of (i) selecting a model parameter of the molecular system; (ii) selecting a validation measure of the molecular system; (iii) simulating the molecular system by the computer modeling with the selected model parameter; (iii) then determining a value of the validation measure of the molecular system from the simulating step; and (iv) testing whether the value of the validation measure is in a predetermined range to validate the computer modeling.

The invention also includes a method for validating a computer modeling of a molecular system, where the steps include (i) selecting a model parameter of the molecular system; (ii) selecting a validation measure of the molecular system; (iii) simulating the molecular system by the computer modeling with the selected model parameter; (iv) then determining a first result of the validation measure of the molecular system from the simulating step; (v) varying the model parameter of the molecular system (vi) simulating the molecular system by the computer modeling with the varied model parameter; (vii) determining a second result of the validation measure of the molecular system from the simulating step; and (viii) determining whether the difference between the first and second results is expected from the variation in the validation measure.

Sardashi, et al., P/N 6,208,137

Sardashi, et al., teach a chemometric method for predicting unknown properties in polymers using measurements of known properties with, e.g., an on-line NMR system. The process includes measuring a particular property in samples from a dataset to form a property data set, obtaining a free induction decay for each the sample to produce a free induction decay data set; analyzing the free induction decay data set using principle component analysis to produce a principle component data set; analyzing the property data set, the free induction decay data set, and the principle component data set using partial-least squares analysis to produce a training data set; and validating the training data set to produce the predictive data set for a predictive calibration model. In other words, the method of Sardashi, et al., uses experimental measurements (e.g., an NMR measurement) of a tangible amount of a physical substance (a polymer) to generate a "training" data set which is then used to develop a mathematical or software model useful for predicting the "macroscopic" physical properties of unknown samples (e.g., predicting the concentration of xylene soluble polypropylene in a sample).

Analysis

The presently-claimed invention is limited to methods for validating computer modeling of a molecular system. The "molecular system" limitation refers to a system where

the behavior of individual molecules is simulated by taking into account forces acting on and/or caused by specific atoms in the molecules being modeled. This definition is clearly supported by the specification (see, e.g., page 10, lines 17-18: "the present methods allow one to assess the significance of estimates of partial charge present on atoms of a molecular system"; page 10, lines 28-29: "the model parameter can be the identity of an atom or group of atoms within a molecule of the molecular system"). The term "molecular system" as used in the present invention does not include macroscopic systems where no such modeling of individual atomic forces is taking place.

The '137 patent deals with the modeling of macroscopic systems. Although the measurement technique used in the preferred embodiment of the '137 patent (NMR) is often used for the qualitative identification of organic compounds and the elucidation of their molecular structure, the methods described in the '137 patent do not use NMR for this purpose. Rather, the '137 patent teaches the use of NMR for quantitative determination of compounds in mixtures and for following the progress of chemical reactions, in particular, for obtaining a "free-induction decay", or "FID" measurements of a sample of material. Measurements, or instrument responses from samples with known concentration levels of a certain component are used to construct a mathematical relationship which relates the instrument response to the concentration of that chemical component. This model may be used to predict the concentration of the chemical component in samples of unknown composition using the measured instrument response(s) from those samples.

Nothing in the '137 patent, however, teaches the application of the methods therein to the modeling or validation of a molecular system, as that term is used in the present invention. Indeed, there is no mention of molecular simulation or molecular modeling anywhere in the '137 patent. As the Federal Circuit articulated in *Brown v. 3M* (265 F.3d 1349, 60 USPQ2d 1375 (Fed. Cir. 2001)), "To anticipate, every element and limitation of the claimed invention must be found in a single prior art reference, arranged as in the claim". All presently-pending claims all contain the limitation that they be applied to validating computer modeling of a molecular system. In view of the foregoing, the Applicants respectfully submit that the rejection of Claims 1, 5, 7, 9, 10, 16-18, and 20 over Sardashi, et

al., is inappropriate and should be withdrawn.

IV. Rejections under 35 U.S.C. §102(b) and §102(e)(2) – Lee, et al.

The Examiner rejected Claims 1-3, 5-9, and 20 under 35 U.S.C. §102(b) and under 35 U.S.C. §102(e)(2) as anticipated by Lee, et al., P/N 5,241,470.

Methods of the Present Invention

All claims rejected by the Examiner as anticipated by Lee, et al., have been amended to include the limitations of originally-presented Claim 7. The amended claims include the steps of (i) selecting a model parameter of the molecular system; (ii) selecting a validation measure of the molecular system, wherein the validation measure is selected from the group consisting of a force between atoms in the molecular system, a bond length or angle between atoms of the molecular system, shape of the molecular system, binding affinity between components of the molecular system, and velocity of atoms of the molecular system; (iii) simulating the molecular system by the computer modeling with the selected model parameter; (iii) then determining a value of the validation measure of the molecular system from the simulating step; and (iv) testing whether the value of the validation measure is in a predetermined range to validate the computer modeling.

Lee, et al., P/N 5,241,470

Lee, et al., teach a method for determining the packing conformation of amino acid side chains on a fixed peptide backbone. Using a steric interaction potential, the side chain atoms are rotated about carbon-carbon bonds such that the side chains preferably settle in a low energy packing conformation. Rotational moves are continued according to a simulated annealing procedure until a set of low energy conformations is identified. The method may be employed, for example, to identify the packing configuration of mutant peptides.

The only "validation" measure used in Lee, et al., to determine a "final" three dimensional peptide conformation is energy. See, e.g., column 1, line 65 through column 2, line 5:

> The invention provides a method for predicting the three dimensional

> conformation of a peptide. This method utilizes the understanding that amino acid side chains of a peptide adopt conformations that maximize favorable atom-atom contacts and minimize unfavorable contacts. With this principle, the method determines the energy of atom-atom interactions and adjusts the amino acid side chain conformations to minimize this energy

In some characterizations (e.g., Claim 1), Lee, et al., use a "side chain steric interaction energy", sometimes termed "steric interaction energy" (e.g., Claim 6), or simply "interaction energy" (e.g., column 2, line 18); in others (e.g., Claim 14), Lee, et al., use a "torsional interaction energy"; in still others (e.g., column 10, line 54), Lee, et al., use a "conformation energy". In column 10, lines 54-61, Lee, et al., disclose that "The conformation energy of a peptide can be modelled in many ways, ranging from potential energy functions having a single van der Waals interaction term, to potential energy functions having many terms that account for torsional biasing, electrostatic interactions, hydrogen bonding, hydrophobic interactions, entropic destabilization, cystine bond formation, and other effects.". Lee, et al., then go on to describe calculations of potential energy using these various terms. However, nowhere in the '470 patent do Lee, et al., suggest the use of such other terms as any type of validation measure.

Claim Amendments

The Applicants have incorporated the limitations of Claim 7 into Claims 1 and 20, thereby changing the scope of Claim 1 to the same scope as that encompassed by originally-filed Claim 7, and narrowing the scope of Claim 20 by the limitations of originally-filed Claim 7.

Claim 10, which was previously dependent on Claim 1, was turned into an independent claim by explicitly inserting the limitations of Claim 1 into Claim 10. This amendment therefore does not in any way change the scope of originally-filed Claim 10.

Analysis

Methods of the present invention are limited to methods of validating where the validation measure is selected from the group consisting of a force between atoms in the molecular system, a bond length or angle between atoms of the molecular system, shape of the molecular system, binding affinity between components of the molecular system, and

velocity of atoms of the molecular system. None of the claims rejected over Lee, et al., encompass methods where the validation measure is energy. Conversely, Lee, et al., teach nothing about the use of measures other than energy for any type of validation of computer modeling of a molecular system. As pointed out above, for anticipation, every element and limitation of the claimed invention must be found in a single prior art reference, arranged as in the claim. In view of the fact that Lee, et al., fail to teach all of the limitations and elements of the invention as amended by the present amendment, the Applicants respectfully submit that the rejection of pending Claims 1-3, 5-9, and 20 over Lee, et al., is inappropriate and should be withdrawn.

V. Informalities

The Examiner has objected to the disclosure because of several blanks on page 4 of the specification. The Applicants have amended the specification to fill in information pertaining to the titles and serial numbers of parent patent applications. This amendment introduces no new matter into the application.

VI. Conclusion

In view of the above amendments and remarks, Applicants submit that this application is in condition for allowance, and such action is respectfully requested. The Examiner is requested to telephone the undersigned if the Examiner does not agree that the application is in condition for allowance.

The Commissioner is hereby authorized to charge any fees (or credit any overpayment) in connection with this Response to Deposit Account No. 50-2599.

Respectfully submitted,

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